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A list of authors and their affiliations appears at the end of the manuscript

ABSTRACT

To dissect the genetic architecture of blood pressure (BP) and assess how its elevation promotes downstream cardiovascular diseases, we analyzed 128,272 SNPs from targeted and genome-wide arrays in 201,529 individuals of European ancestry. Genotypes from an additional 140,886 individuals of European ancestry were used as validation for loci reaching genome-wide significance but without prior support in the literature. We identified 66 BP loci, of which 17 were novel and 15 harbored multiple distinct association signals, and which together explain up to 3.5% of BP variation. The 66 index SNPs were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells, consistent with a primary role in BP control through modulating blood vessel tone and fluid filtration across multiple tissues, not solely the kidney. Importantly, the 66 index SNPs combined in a risk score showed comparable effects in 64,421 individuals of non-European descent (South-Asian, East-Asian and African), confirming that these are ancestral physiological effects that arose prior to human migration out of Africa. The 66-SNP BP risk score was significantly associated with target-organ damage in multiple tissues, with minor effects in the kidney. Our data expand current knowledge of BP pathways, and also, highlight that BP regulation and its effects may occur in multiple organs and tissues beyond the classic renal system.

There are considerable physiological, clinical and genetic data that implicate the kidney as the major regulator of BP through maintaining salt-water balance and that renal damage is consequent to long-term BP elevation. However, alternative hypotheses, such as increasing systemic vascular resistance, are also serious contenders to explain the rise of BP with increasing age. The genetic basis of elevated blood pressure or hypertension (HTN) involves many loci that have been identified using large-scale analyses of candidate genes[1,2], linkage studies, and genome-wide association studies (GWAS)[3-12]. The genes underlying BP regulation can help resolve many of the open questions regarding BP (patho-) physiology. While ~40-50% of BP variability is heritable[13,14], the identified genetic variation explains only ~2%[1-12]. This is considerably less than that observed for other cardiovascular disease (CVD) risk factors, such as plasma lipid fractions, despite the fact that they have comparable heritability[15]. The sources of this discrepancy could be many, but the major reasons are likely to be the constraints on physiological variation of BP and contributions from diverse organs and tissues, potentially resulting in hundreds or thousands of genetic variants of weak effects. Consequently, the fundamental causes of hypertension susceptibility also remain unknown.

The Cardio-MetaboChip is a custom genotyping microarray designed to facilitate cost-effective follow-up of nominal associations for metabolic and cardiovascular traits, including BP. This array comprises 196,725 variants, including ~5,000 SNPs with nominal (P <0.016) evidence of BP association in our previous GWAS meta-analysis[5]. Furthermore, the array includes several dense scaffolds for fine mapping of selected loci spanning, on average, genomic regions of 350 kilobases[5,16], of which 24 include genome-wide significant BP association in the current study[5,16]. Here we performed BP GWAS meta-analysis of both systolic (SBP) and diastolic (DBP) BP using data from 109,096 individuals directly genotyped using the Cardio-MetaboChip array, in combination with imputed data from an additional 92,433 individuals with genome-wide genotyping, all of European (EUR) ancestry. Validation of loci reaching genome-wide significance but without previous support in the literature was sought using association results from an additional 140,886 individuals of European ancestry from the UK Biobank. We assessed whether the genome-wide significant BP SNPs identified, which are largely in non-coding DNA, were associated with expression levels of nearby genes, and tested for enrichment of BP SNPs in *cis*-regulatory sequences. Signal refinement and analyses of associated variants were performed in 64,421 individuals of South-Asian (SAS), East-Asian (EAS), and African (AFR) ancestry to assess their global distribution. Finally, a genotype risk score was constructed to examine the impact of the BP SNPs on cardiovascular and other end-organ outcomes.

RESULTS

Novel genetic loci associated with SBP and DBP

We performed meta-analyses of association summary statistics from a total of 201,529 individuals of EUR ancestry from 74 studies: (i) 109,096 individuals from 46 studies genotyped on Cardio-MetaboChip; and (ii) 92,433 individuals from 28 studies with imputed genotype data from genome-wide genotyping at SNPs overlapping the variants on Cardio-MetaboChip. Twenty-four of the 28 studies with genome-wide genotyping data had contributed to previous analyses (**Supplementary Tables 1-3**)[5,7].

BP was measured using standardized protocols in all studies (**Supplementary Table 1**), regardless of whether the primary focus was BP or another trait. We initially analyzed affected and unaffected individuals from samples selected as cases (e.g. type 2 diabetes) or controls, separately. However, because sensitivity analyses did not reveal any significant difference in BP effect size estimates between case and control samples (data not shown), we analyzed all samples combined. When available, the average of two BP measurements was used for association analyses (**Supplementary Table 1**). If an individual was taking a BP-lowering treatment, the underlying SBP and DBP were estimated by adding 15 mmHg and 10 mmHg, respectively, to the measured values, as done in prior analyses[5,17]. Association statistics, in models adjusting for age, age^2, sex, and body mass index (BMI), were obtained for each study separately, with genomic control applied to correct for study-specific population structure. Fixed-effects meta-analysis proceeded in 4 stages, separately for the following associations: Stage 1, using results based on 46 studies using Cardio-MetaboChip genotypes of 109,096 participants; Stage 2, using additional results based on imputed genotypes from genome-wide genotyping arrays in 4 previously unpublished studies; Stage 3 using imputed genotypes from genome-wide genotyping arrays in 24 previously published studies[5]; and Stage 4, the joint meta-analysis of Stages 1-3 including a total of 201,529 independent individuals (**Supplementary Figure 1, Supplementary Tables 2-3, Supplementary Note**). To account for population structure between studies in Stages 1-3 of our meta-analysis, genomic control correction was applied in each of these stages. The "double" genomic control correction applied is the same approach as other published large-scale studies of quantitative cardio-metabolic traits that combine genotype data from GWAS and Cardio-MetaboChip [18,19].

At stage 4, 67 loci attained genome-wide significance ($P < 5 \times 10^{-8}$), 18 of which without prior support in the literature (**Supplementary Table 4**). Quantile-quantile plots (**Supplementary Figure 2**) of

the stage 4 meta-analysis showed an excess of small *P* values, with an elevated genomic control lambda estimate that were persistent, albeit attenuated, after excluding all 66 loci. This observation is compatible with either residual uncorrected population stratification or the presence of a large number of variants that are truly associated with BP but fail to achieve genome-wide significance in the current meta-analysis. The Cardio-MetaboChip array's inclusion of SNPs from a prior BP GWAS[5] does not appear to be the sole explanation, as we did not observe a significant decrease of the excess of small *P* values when we excluded all SNPs that were selected based on BP for the Cardio-MetaboChip. Given that the quantile-quantile plots continued to show deviation from the null expectation even after removing new, known, and additional variants related to BP (**Supplementary Figures 3 and 4**), we sought additional validation to support variants (N=18) attaining genome-wide significance, but without prior support in the literature, in up to 140,886 individuals of European ancestry from UK Biobank[20]. For these SNPs, stage 5 meta-analysis combined association summary statistics from stage 4 and UK Biobank, in a total of 342,415 individuals (**Supplementary Table 5**).

Upon stage 5 meta-analysis, 17 of 18 variants retained genome-wide significance for the primary trait (SBP or DBP result with lower *P* value). The one variant that was not genome-wide significant had a borderline *P* value of 4.49×10^{-8} at stage 4. These findings are consistent with appropriate calibration of the association test statistics at stage 4 such that observing one failure among 18 validation tests is consistent with the use of a threshold designed ($P < 5 \times 10^{-8}$) to have a 1 in 20 chance of a result as or more extreme solely due to chance.

In total, 66 loci attained genome-wide significance: 13 loci for SBP only, 12 loci for DBP only, and 41 for both traits. Of these, 17 BP loci were novel, while 49 were previously reported at genome-wide significance (**Table 1**). The new loci were defined based on mapping >1Mb from any previously established locus, with the exception of one region characterized by long-range LD spanning several mega-bases, which was considered a single locus. Plots of association results across the genome show the genomic features of each locus and SNP *P* values, with loci labeled arbitrarily according to the gene(s) nearest the lead SNP (**Figure 1**).

Compared with previous BP variants[5,7,21], the average absolute effect size of the newly discovered variants is smaller, although the minor allele frequency (MAF) is comparable, presumably owing to the increased power of a larger sample size (**Figure 2**). As expected from the high correlation between SBP and DBP values, the observed directions of effects for the two traits were generally concordant (**Supplementary Figure 5**), and the absolute effect sizes were inversely correlated with MAF (**Table 1** and **Supplementary Figure 6**). The 66 BP SNPs explained 3.46% and 3.36% of SBP and DBP

variance, respectively, an increase from 2.95% and 2.78% for SBP and DBP for the 49 previously reported SNPs alone (**Supplementary Note**). The low percent of variance explained is consistent with earlier estimates of large numbers of common variants of weak effects and a large number of genes influencing BP levels[5].

Signal refinement at the 66 BP loci

Quantitative trait associations are often reported in the literature based on a single index SNP, despite the fact that linkage disequilibrium (LD) to the causal variant can implicate many nearby variants. To identify distinct signals of association at the 66 BP loci and the variants most likely to be causal for each, we started with an approximate conditional analysis using a model selection procedure implemented in the GCTA-COJO package[22,23] as well as a detailed literature review of all published BP association studies. GCTA-COJO analysis was performed using the association summary statistics for SBP and DBP from the Stage 4 EUR ancestry meta-analyses, with the LD between variants estimated on the basis of Cardio-MetaboChip genotype data from 7,006 individuals of EUR ancestry from the GoDARTS cohort[24]. More than one distinct BP association signal was identified at 13 loci at $P < 5 \times 10^{-8}$ (**Supplementary Table 6**, **Supplementary Figures 7, and Supplementary Note**). At six loci, the distinct signals were identified in separate analyses of both SBP and DBP; these trait-specific associations were represented by the same or highly correlated ($r^2 > 0.8$) SNPs at 5 of the 6 loci (**Supplementary Tables 7-8**). We repeated GCTA-COJO analyses using the same summary association results, but with a different reference sample for LD estimates (WTCCC1-T2D/58BC, N = 2,947, **Supplementary Note**) and observed minimal differences arising from minor fluctuations in the association *P* value in the joint regression models (**Supplementary Table 7-8**). LD-based comparisons of published association signals at established BP loci, and the current study's findings suggested that at 10 loci, the signals identified by the single-SNP and the GCTA-COJO analyses were distinct from those in the literature (**Supplementary Table 9**).

We then performed multivariable regression modeling in a single large cohort (Women's Genome Health Study, WGHS, N = 23,047) with simultaneous adjustment for 1) all combinations of putative index SNPs for each distinct signal from the GCTA-COJO conditional analyses, and 2) all index SNPs for all potential distinct signals identified by our literature review (**Supplementary Table 9, Supplementary Note**). Although WGHS is very large as a single study, power is reduced in a single sample compared to that in the overall meta-analysis (23k vs. 201k individuals) and consequently the failure to reach significance does not represent non-replication for individual SNPs. The WGHS analysis

supported two distinct signals of association from the GCTA-COJO analysis at eight of 13 loci, but could not provide support for the remaining five loci (**Supplementary Table 10**). The joint SNP modeling in WGHS, however, indicated two distinct signals of association at three additional loci (*GUCY1A3-GUCY1B3*, *SYNPO2L* and *TBX5-TBX3*), at which the SNP identified in the current study is distinct from that previously reported in the literature[5,11].

Established loci often extend over hundreds of kilobases and contain many genes that could plausibly underlie the BP association. We sought to refine the localization of likely functional variants at loci with high-density coverage on the Cardio-MetaboChip. We followed a Bayesian approach and used the association summary statistics from the EUR ancestry meta-analyses to define, for each signal, credible sets of variants that have 99% probability of containing or tagging the causal variant (**Supplementary Note**). To improve the resolution of the method, the analyses were restricted to 24 regions selected to fine-map (FM) genetic associations, and that included at least one SNP reaching genome-wide significance in the current meta-analyses (**Supplementary Table 11**). Twenty-one of the Cardio-MetaboChip FM regions were BP loci in the original design, with three of the newly discovered BP loci in FM regions that were originally selected for other traits. We observed that the 99% credible sets at five BP loci spanned a small region, <10 kb (*PLCE1* and *SLC39A8* for SBP and DBP; *FGF5* for SBP, with <20kb for DBP; *JAG1* and *ZC3HC1* for DBP, with <20kb for SBP). The greatest refinement was observed at the *SLC39A8* locus for SBP and DBP, and at the *ZC3HC1* and *PLCE1* loci for DBP, where the 99% credible sets included only the index variants (**Supplementary Table 12**). Although credible sets mapped primarily to non-coding sequence, they included one synonymous and seven non-synonymous variants that attained high posterior probability of driving seven distinct association signals at six BP loci (**Supplementary Table 12**). Of these, three variants alone account for more than 95% of the posterior probability of driving the association signal observed at each of three loci: rs13107325 at the *SLC39A8* locus with posterior probability 99.4% for SBP and nearly 100% for DBP; rs1800562 at the *HFE* locus accounting for 98.1% of the posterior probability for DBP; and rs11556924 at the *ZC3HC1* locus with posterior probability 97.8% for SBP and 99.9% for DBP. Despite reduced statistical power, the analyses restricted to the samples with Cardio-MetaboChip genotypes only (N = 109,096) identified as credible causal SNPs the majority of those identified in the analyses of the GWAS+Cardio-MetaboChip data (**Supplementary Table 12**). Given that the Cardio-MetaboChip-only data included more eligible SNPs, a larger number of credible causal SNPs were identified. The full list of SNPs in the 99% credible sets are listed in **Supplementary Table 13**.

What do the BP SNPs do?

Index SNPs or their proxies ($r^2 > 0.8$) altered amino acid sequence at 11 of 66 BP loci (**Table 1**). Thus, the majority of BP-association signals are likely driven by non-coding variants hypothesized to regulate expression of some nearby gene in *cis*. To identify their effects we first sought SNPs associated with gene expression (eSNPs) from a range of available expression data which included hypertension target end organs and cells of the circulatory system (heart tissue, kidney tissue, brain tissue, aortic endothelial cells, blood vessels) and other tissue/cell types ($CD4^+$ macrophages, monocytes lymphoblastoid cell lines, skin tissue, fat tissue, and liver tissue). Fourteen BP SNPs at the *MTHFR-NPPB*, *MDM4*, *ULK4*, *CYP1A1-ULK3*, *ADM, FURIN-FES, FIGN,* and *PSMD5* loci were eSNPs across different tissues (**Supplementary Table 14)**. Of these 14 eSNPs, three were predicted to alter the amino acid sequence at the *MTHFR-NPPB*, *MAP4* and *ULK4* loci, providing two potential mechanisms to explore in functional studies. Second, we used gene expression levels measured in whole blood in two different samples each including >5,000 individuals of EUR descent. We tested whether the lead BP SNP was associated with expression of any transcript in *cis* (<1Mb from the lead SNP at each locus) at a false discovery rate (FDR) of < 0.05, accounting for all possible *cis*-transcript association tests genome-wide. It is likely that we did not genotype the causal genetic variant underlying a BP association signal. A nearby SNP-transcript association, due to LD, may therefore reflect an independent genetic effect on expression that is unrelated to the BP effect. Consequently, we assumed that the lead BP SNP and the most significant eSNP for a given transcript should be highly correlated ($r^2 > 0.7$). Furthermore, we assumed that the significance of the transcript association with the lead BP SNP should be substantially reduced in a conditional model adjusting for the best eSNP for a given transcript. Eighteen SNPs at 15 loci were associated with 22 different transcripts, with a total of 23 independent SNP-transcript associations (three SNPs were associated with two transcripts each, **Supplementary Table 15, Supplementary Note**). The genes expressed in a BP SNP allele-specific manner are clearly high-priority candidates to mediate the BP association. In whole blood, these genes included obvious biological candidates such as *GUCY1A3*, encoding the alpha subunit of the soluble guanylate cyclase protein, and *ADM*, encoding adrenomedullin, both of which are known to induce vasodilation[25,26]. There was some overlap of eSNPs between the whole blood and other tissue datasets at the *MTHFR-NPPB*, *MDM4*, *PSMD5*, *ULK4* and *CYP1A1-ULK3* loci, illustrating additional potentially causal genes for further study (*MTHFR* and *CLCN6*, *MDM4*, *PSMD5*, *ULK4*, *CYP1A1*, and *ULK3*).

An alternative method for understanding the effect on BP of non-coding variants is to determine whether they fall within DNaseI hypersensitivity sites (DHSs). DHSs represent open regions of chromatin

that are accessible to protein binding and can indicate transcriptional activity. We performed two analyses to investigate whether BP SNPs or their LD proxies ($r^2 > 0.8$) were enriched in DHSs in a cell-type-specific manner (**Supplementary Note**). First, we used Epigenomics Roadmap and ENCODE DHS data from 123 adult cell lines or tissues[27-29] to estimate the fold increase in the proportion of BP SNPs mapping to DHSs compared to SNPs associated at genome-wide significance with non-BP phenotypes from the NHGRI GWAS catalog[30]. We observed that 7 out of the 10 cell types with the greatest relative enrichment of BP SNPs mapping to DHSs were from blood vessels (vascular or micro-vascular endothelial cell-lines or cells) and 11 of the 12 endothelial cells were among the top quarter most enriched among the 123 cell types (**Figure 3** and **Supplementary Table 16**). In a second analysis of an expanded set of tissues and cell lines, in which cell types were grouped into tissues (**Supplementary Table 17**), BP-associated SNP enrichment in DHSs in blood vessels was again observed ($P = 1.2 \times 10^{-9}$), as well as in heart samples ($P = 5.3 \times 10^{-8}$; **Supplementary Table 18**).

We next tested whether there was enrichment of BP SNPs in H3K4me3[31] sites, a methylation mark associated with both promoter and enhancer DNA. We observed significant enrichment in a range of cell types including CD34 primary cells, adult kidney cells, and muscle satellite cultured cells (**Supplementary Table 19)**. Enrichment of BP SNPs in predicted strong and weak enhancer states and in active promoters[32] in a range of cell types was also observed (**Supplementary Table 20, Supplementary Figure 8**).

We used Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA)[33] to attempt to identify pathways over-represented in the BP association results. No gene sets meeting experiment-wide significance for enrichment for BP association were identified by MAGENTA after correction for multiple testing, although some attained nominal significance (**Supplementary Table 21**, **Supplementary Note**). We also adapted the DEPICT[34] pathway analysis tool (Data-driven Expression Prioritized Integration for Complex Traits) to identify assembled gene-sets that are enriched for genes near associated variants, and to assess whether genes from associated loci were highly expressed in particular tissues or cell types. Using the extended BP locus list based on genome-wide significant loci from this analysis and previously published SNPs that may not have reached genome-wide significance in the current analysis (**Supplementary Table 9**), we identified six significant (FDR ≤ 5%) gene sets: embryonic growth retardation, abnormal cardiovascular system physiology, abnormal cardiac muscle contractility, SNTB1 protein complex, G Alpha 1213 signaling events, and prolonged QRS complex duration. We also found that suggestive SBP and DBP associations ($P < 1 \times 10^{-5}$) were enriched for reconstituted gene-sets at DBP loci (mainly related to developmental pathways), but not at SBP loci

(**Supplementary Table 22**, **Supplementary Note**). In a final analysis, we assessed Cardio-MetaboChip SNPs at the fine-mapping loci using formaldehyde-assisted isolation of regulatory elements (FAIRE-gen) in lymphoblastoid cell lines[35]. Our results provided support for two SNPs, one of which SNP (rs7961796 at the *TBX5-TBX3* locus) was located in a regulatory site. Although the other SNP (rs3184504 at the *SH2B3* locus) is a non-synonymous variant, there was also a regulatory site indicated by DNaseI and H3K4me1 signatures at the locus, making the SNP a potential regulatory variant (**Supplementary Table 23**)[36]. Both SNPs were included in the list of 99% credible SNPs at each locus.

Asian- and African ancestry BP SNP association

We tested the 66 lead SNPs at the established and novel loci for association with BP in up to 20,875 individuals of South Asian (SAS) ancestry, 9,637 individuals of East Asian (EAS) ancestry, and 33,909 individuals of AFR ancestry. As expected, the effect allele frequencies are very similar across studies of the same ethnicity, but markedly different across different ancestry groups (**Supplementary Figure 9**). Many associations of individual SNPs failed to reach $P < 0.05$ for the BP trait with the lower P value (**Supplementary Table 24**), which could potentially be due to the much lower statistical power at the sample sizes available, different patterns of LD at each locus across ancestries, variability in allele frequency, or true lack of association in individuals of non-European ancestry. The low statistical power for the great majority of SNPs tested is visible considering SNP-by-SNP power calculations using European ancestry effect sizes (**Supplementary Table 24**). However, concordant directions of allelic effects for both SBP and DBP were observed for 45/66 SNPs in SAS, 36/60 SNPs in EAS, and 42/66 SNPs in AFR samples: the strongest concordance with SAS is not surprising because South Asians are more closely related to Europeans than are East Asians or Africans. Moreover, strong correlation of effect sizes was observed between EUR samples with SAS, EAS, or AFR samples (r = 0.55, 0.60, and 0.48, respectively). To test the overall effect of ancestry, where the BP effect may be detectable at only a subset of SNPs, a more powerful test is to construct a combined risk score weighted by allele-specific effects across 66 index SNPs, separately for SBP and DBP, as a predictor of BP in each population sample. A shortcoming of the use of a score test aggregating effects across multiple variants is that they obscure the subset of variants that does not show reliable association in multiple ethnicities. The score represents the predicted mm Hg change for an individual based on their genotype at all 66 SNPs. The SBP and DBP risk scores were significant predictors of SBP and DBP, respectively, in all samples. The change in risk score associated with a 1 mm Hg higher SBP/DBP in EUR samples was associated with a 0.58/0.50 mm Hg higher SBP/DBP in SAS samples (SBP $P = 1.5 \times 10^{-19}$, DBP $P = 3.2 \times 10^{-15}$), 0.49/0.50 mm

Hg SBP/DBP in EAS samples (SBP $P = 1.9 \times 10^{-10}$, DBP $P = 1.3 \times 10^{-7}$), and 0.51/0.47 mm Hg SBP/DBP in AFR samples (SBP $P = 2.2 \times 10^{-21}$, DBP $P = 6.5 \times 10^{-19}$). The attenuation of the genetic risk score estimates in non-European ancestries is presumably due to inclusion of a subset of variants that lack association in the non-European samples. In the admixed populations tested (mainly African ancestry studies), the degree of European admixture influences the extent of association. We subsequently performed a trans-ethnic meta-analysis of the 66 SNPs in all 64,421 samples across the three non-European ancestries. After correcting for 66 tests, 12/66 SNPs were significantly associated with either SBP or DBP ($P < 7.6 \times 10^{-4}$), with a correlation of EUR and non-EUR effect estimates of 0.77 for SBP and 0.67 for DBP; the European-ancestry SBP or DBP risk score was associated with 0.53/0.48 mm Hg higher BP per predicted mm Hg SBP/DBP respectively (SBP $P < 6.6 \times 10^{-48}$, DBP $P < 1.3 \times 10^{-38}$). For 7 of the 12 significant SNPs, no association has previously been reported in genome-wide studies of non-European ancestry. While some heterogeneity of effects was observed between European and non-European effect estimates (Cochran's Q p-value <0.05 for 30/132 tests), these were not distinguishable from chance effects when considering a multiple test correction (**Supplementary Table 24**). Taken together, these findings suggest that, in aggregate, BP loci identified using data from individuals of EUR ancestry are also predictive of BP in non-EUR samples, but larger non-European sample sizes will be needed to establish precisely which individual SNPs are associated in a given ethnic group.

Impact on hypertensive target organ damage

Long-term elevated BP causes target organ damage, especially in the heart, kidney, brain, large blood vessels, and the retinal vessels[37]. Consequently, the genetic effect of the 66 SBP and DBP SNPs on end-organ outcomes can be directly tested using the risk score, although some outcomes lacked results for a small number of SNPs. Interestingly, BP risk scores significantly predicted (**Supplementary Note**) coronary artery disease risk, left ventricular mass and wall thickness, stroke, urinary albumin/creatinine ratio, carotid intima-medial thickness and central retinal artery caliber, but not heart failure or other kidney phenotypes, after accounting for the number of outcomes examined (**Table 2**). Some SNPs could contribute to the risk score with effects that are stronger or weaker than their BP effects would suggest when considering all BP variants collectively. We sought to test the robustness of our risk scores to removal of SNPs with such outlier effects. We therefore repeated the risk score analysis removing iteratively SNPs that contributed to statistical heterogeneity (SNP trait effects relative to SNP BP effects). Heterogeneity was defined based on a multiple testing adjusted significance threshold for Cochran's Q test of homogeneity of effects (**Supplementary Note**). The risk score analyses restricted to the subset of

SNPs showing no heterogeneity of effect revealed essentially identical results, with the exception that urinary albumin/creatinine ratio was no longer significant. The per-SNP results are provided in **Supplementary Table 25** and **Supplementary Figures 10.** Because large-scale GWAS of non-BP cardiovascular risk factors are available, we examined the BP risk scores as predictors of other cardiovascular risk factors: LDL-cholesterol, HDL-cholesterol, triglycerides, type 2 diabetes, BMI, and height. We observed nominal (P <0.05) associations of the BP risk scores with risk factors, although mostly in the opposite direction to the risk factor-CVD association (**Supplementary Table 26**). The failure to demonstrate an effect of hypertension on heart failure may reflect power from a modest sample size, but the lack of significant effects on renal measures suggests that the epidemiologic relationship of higher BP and worse renal function may not reflect direct consequences of BP elevation.

DISCUSSION

The study reported here is the largest to date to investigate the genomics of BP in multiple continental ancestries. Our results highlight four major features of inter-individual variation in BP: (1) we identified 66 (17 novel) genome-wide significant loci for SBP and DBP by targeted genotyping of up to 342,415 individuals of European ancestry that cumulatively explain ~3.5% of the trait variance (novel loci validated using data from additional 140,886 individuals); (2) the variants were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells; (3) the variants had broadly comparable BP effects in South Asians, East Asian and Africans, albeit in smaller sample sizes; and, (4) a 66 SNP risk-score predicted target organ damage in the heart, cerebral vessels, carotid artery and the eye with little evidence for an effect in kidneys. Overall, there was no enrichment of a single genetic pathway in our data; rather, our results are consistent with the effects of BP arising from multiple tissues and organs.

Genetic and molecular analyses of Mendelian syndromes of hypertension and hypotension point to a renal origin, involving multiple rare deleterious mutations in proteins that regulate salt-water balance[38]. This is strong support for Guyton's hypothesis that the regulation of sodium excretion by the kidney and its effects on extracellular volume is the main pathway determining intra-arterial pressure[39]. However, our genetic data from unselected individuals in the general community argues against a single dominant renal effect.

First, the 66 SNPs we identified are not chance effects, but have a global distribution and impact on BP that are consistent as measured by their effects across the many studies meta-analyzed. That they are polymorphic across all continental ancestries argues for their origin and functional effects prior to human continental differentiation.

The adrenergic autonomic system has been considered an important mediator of BP regulation, and is targeted by beta-adrenergic antagonists for the treatment of hypertension. The SNP rs6271 lies within the coding sequence of the dopamine beta hydroxylase gene (*DBH*), encoding the enzyme that catalyzes the conversion of dopamine to norepinephrine, a critical neurotransmitter and effector of sympathetic control of BP. The variant results in an arginine to cysteine amino acid change at the highly conserved position 549 (R549C) and is predicted to be potentially damaging by Polyphen2. Rare loss-of-function mutations in this gene are associated with low plasma dopamine beta hydroxylase activity, low plasma norepinephrine and high plasma dopamine, and a clinical syndrome including orthostatic hypotension[40,41]. Several of the 17 novel loci contain other strong biological candidates; these are described in greater detail in **Supplementary Table 27 and** the **Supplementary Note**.

The single most common feature we identified was the enrichment of regulatory elements for gene expression in vascular endothelial cells. The broad distribution of these cells across both large and small vessels and across all tissues and organs suggest that functional variation in these cells affect endothelial permeability or vascular smooth muscle cell contractility via multiple pathways. These hypotheses will need to be rigorously tested, in appropriate models, to assess the contribution of these pathways to BP control, and these pathways could be targets for systemic anti-hypertensive therapy as they are for the pulmonary circulation[42]. In summary, the genetic observations will contribute to a new and improved understanding of BP biology and a re-evaluation of the pathways considered relevant for therapeutic BP control.

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SUPPLEMENTARY NOTE

Supplementary Note is available in the online version of the paper.

ACKNOWLEDGEMENTS

We thank all the study participants of this study for their contributions. Detailed acknowledgment of funding sources is provided in the **Supplementary Note.**

AUTHOR CONTRIBUTIONS

See Supplementary Note for Author Contributions.

AUTHOR INFORMATION

The authors declare competing financial interests (see corresponding section in the **Supplementary Note).**

TABLE LEGENDS

Table 1. SBP and DBP association at 66 loci.

Meta-analysis results of up to 342,415 individuals of European ancestry for SBP and DBP: Established and new loci are grouped separately. Nearest genes are shown as locus labels but this should not be interpreted as support that the causal gene is the nearest gene. The lead SNP with the lowest *P* value for either BP trait is shown as the lead SNP and both SBP and DBP results are presented even if both are not genome-wide significant. The SNP effects are shown according to the effect in mm Hg per copy of the coded allele (that is the allele coded 0, 1, 2) under an additive genetic model. "*" in the lead SNP column indicates a non-synonymous coding SNP (either the SNP itself or another SNP in r^2 >0.8). # Established loci have smaller total sample sizes relative to novel loci (see **Supplementary Note**).

Table 2. Prediction of hypertensive target organ damage by a multi-BP SNP score.

Shown are the estimated effects of a BP risk score comprised of up to 66 SNPs (see column "Total #SNPs") on risk of dichotomous outcome (as odds ratios) or increment in continuous measures per predicted mmHg of the SBP or DBP score. The effect sizes are expressed as incremental change in the phenotype for quantitative traits and natural logarithm of the odds ratio for binary traits, per 1 mmHg predicted increase in SBP or DBP. *P* values are bolded if they meet an analysis-wide significance threshold (< 0.05/18 = 0.0028). Results for all SNPs ("all") and for pruned results ("p") are shown. The pruned results were obtained by iterative removal of SNPs from the risk score starting with the SNP with lowest heterogeneity *P* value. Iterations to remove SNPs were continued until the heterogeneity *P* value was < 0.0028 (see **Supplementary Note**). The number of SNPs removed when calculating the pruned results is indicated by "# SNPs rem.". The results per individual SNP can be found in **Supplementary Table 15**. CAD: coronary artery disease, LV: left ventricle, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, cr: creatinine, cIMT: carotid intima: media thickness. Var. type denotes the variable type and cont. for continuous, or dic. for dichotomous. Eth. = Ethnicity, Consort. = Consortium, EUR = European ancestry, EAS = East Asian ancestry.

1 Table 1. New and known BP loci.

Locus no.	Locus name	Lead SNP	Chr	Position (hg19)	CA /NC	Coded allele freq	Traits	SBP				DBP			
								Effect	SE	*P* value	Total N	Effect	SE	*P* value	Total N#
NEW 1	***HIVEP3***	rs7515635	1	42,408,070	T/C	0.468	**SBP**	**0.307**	**0.0444**	**4.81E-12**	**340,969**	0.1365	0.0263	2.05E-07	340,934
NEW 2	***PNPT1***	rs1975487	2	55,809,054	A/G	0.464	**DBP**	-0.2107	0.045	2.81E-06	337,522	**-0.1602**	**0.0266**	**1.75E-09**	**337,517**
NEW 3	***FGD5***	rs11128722	3	14,958,126	A/G	0.563	**SBP** & DBP	**-0.3103**	**0.0469**	**3.61E-11**	**310,430**	**-0.1732**	**0.0279**	**5.16E-10**	**310,429**
NEW 4	***ADAMTS9***	rs918466	3	64,710,253	A/G	0.406	**DBP**	-0.0865	0.0459	5.94E-02	336,671	**-0.1819**	**0.027**	**1.73E-11**	**336,653**
NEW 5	***TBC1D1-FLJ13197***	rs2291435	4	38,387,395	T/C	0.524	**SBP** & DBP	**-0.3441**	**0.0449**	**1.90E-14**	**331,382**	**-0.156**	**0.0266**	**4.26E-09**	**331,389**
NEW 6	***TRIM36***	rs10077885	5	114,390,121	A/C	0.501	SBP & **DBP**	**-0.284**	**0.0444**	**1.64E-10**	**338,328**	**-0.1735**	**0.0263**	**3.99E-11**	**338,323**
NEW 7	***CSNK1G3***	rs6891344	5	123,136,656	A/G	0.819	**DBP**	0.2811	0.058	1.24E-06	338,688	**0.2311**	**0.0343**	**1.58E-11**	**338,678**
NEW 8	***CHST12-LFNG***	rs2969070	7	2,512,545	A/G	0.639	SBP & **DBP**	**-0.2975**	**0.0464**	**1.44E-10**	**335,991**	**-0.1821**	**0.0274**	**2.92E-11**	**335,972**
NEW 9	***ZC3HC1***	rs11556924	7	129,663,496	T/C	0.384	SBP & **DBP**	**-0.2705**	**0.0468**	**7.64E-09**	**325,929**	**-0.2141**	**0.0276**	**8.15E-15**	**325,963**
NEW 10	***PSMD5***	rs10760117	9	123,586,737	T/G	0.415	**SBP**	**0.283**	**0.0457**	**6.10E-10**	**333,377**	0.0999	0.0269	2.08E-04	333,377
NEW 11	***DBH***	rs6271*	9	136,522,274	T/C	0.072	SBP & **DBP**	**-0.5911**	**0.0899**	**4.89E-11**	**306,394**	**-0.4646**	**0.0532**	**2.42E-18**	**306,463**
NEW 12	***RAPSN, PSMC3, SLC39A13***	rs7103648	11	47,461,783	A/G	0.614	SBP & **DBP**	**-0.3349**	**0.0462**	**4.43E-13**	**335,614**	**-0.2409**	**0.0272**	**9.03E-19**	**335,592**
NEW 13	***LRRC10B***	rs751984	11	61,278,246	T/C	0.879	SBP & **DBP**	**0.4074**	**0.0691**	**3.80E-09**	**334,583**	**0.3755**	**0.0409**	**4.20E-20**	**334,586**
NEW 14	***SETBP1***	rs12958173	18	42,141,977	A/C	0.306	**SBP** & DBP	**0.3614**	**0.0489**	**1.43E-13**	**331,007**	**0.1789**	**0.0289**	**5.87E-10**	**331,010**
NEW 15	***INSR***	rs4247374	19	7,252,756	T/C	0.143	SBP & **DBP**	**-0.5933**	**0.0673**	**1.23E-18**	**302,458**	**-0.3852**	**0.0396**	**2.08E-22**	**302,459**
NEW 16	***ELAVL3***	rs17638167	19	11,584,818	T/C	0.047	**DBP**	-0.4784	0.1066	7.13E-06	333,137	**-0.3479**	**0.0632**	**3.71E-08**	**333,107**
NEW 17	***CRYAA-SIK1***	rs12627651	21	44,760,603	A/G	0.288	**SBP** & DBP	**0.3905**	**0.0513**	**2.69E-14**	**310,738**	**0.2037**	**0.0301**	**1.36E-11**	**310,722**
EST 1	***CASZ1***	rs880315	1	10,796,866	T/C	0.641	**SBP** & DBP	**-0.475**	**0.062**	**2.09E-14**	**184,226**	**-0.257**	**0.038**	**1.34E-11**	**184,212**
EST 2	***MTHFR-NPPB***	rs17037390	1	11,860,843	A/G	0.155	**SBP** & DBP	**-0.908**	**0.081**	**5.95E-29**	**195,493**	**-0.499**	**0.05**	**1.20E-23**	**195,481**
EST 3	***ST7L-CAPZA1-MOV10***	rs1620668	1	113,023,980	A/G	0.822	**SBP** & DBP	**-0.535**	**0.076**	**1.45E-12**	**197,966**	**-0.285**	**0.047**	**9.00E-10**	**197,948**
EST 4	***MDM4***	rs4245739	1	204,518,842	A/C	0.737	**DBP**	0.326	0.068	1.37E-06	191,594	**0.243**	**0.041**	**4.63E-09**	**191,578**
EST 5	***AGT***	rs2493134*	1	230,849,359	T/C	0.579	SBP & **DBP**	**-0.413**	**0.058**	**9.65E-13**	**199,505**	**-0.275**	**0.036**	**9.53E-15**	**199,502**
EST 6	***KCNK3***	rs2586886	2	26,932,031	T/C	0.599	SBP & **DBP**	**-0.404**	**0.059**	**5.94E-12**	**197,269**	**-0.254**	**0.036**	**1.92E-12**	**197,272**
EST 7	***NCAPH***	rs772178	2	96,963,684	A/G	0.64	**DBP**	-0.072	0.061	2.39E-01	192,513	**-0.208**	**0.038**	**3.58E-08**	**192,501**
EST 8	***FIGN-GRB14***	rs1371182	2	165,099,215	T/C	0.443	**SBP** & DBP	**-0.444**	**0.058**	**1.89E-14**	**196,262**	**-0.252**	**0.036**	**1.50E-12**	**196,240**
EST 9	***HRH1-ATG7***	rs2594992	3	11,360,997	A/C	0.607	**SBP**	**-0.334**	**0.06**	**2.31E-08**	**189,895**	-0.136	0.037	2.20E-04	189,854
EST 10	***SLC4A7***	rs711737	3	27,543,655	A/C	0.604	**SBP**	**0.334**	**0.058**	**9.93E-09**	**200,282**	**0.17**	0.036	2.24E-06	200,260
EST 11	***ULK4***	rs2272007*	3	41,996,136	T/C	0.18	**DBP**	-0.11	0.077	1.52E-01	193,915	**0.328**	**0.047**	**3.94E-12**	**193,900**
EST 12	***MAP4***	rs6442101*	3	48,130,893	T/C	0.692	SBP & **DBP**	**0.396**	**0.062**	**1.62E-10**	**200,543**	**0.303**	**0.038**	**1.60E-15**	**200,534**
EST 13	***MECOM***	rs6779380	3	169,111,915	T/C	0.539	**SBP** & DBP	**-0.439**	**0.06**	**1.85E-13**	**186,535**	**-0.239**	**0.037**	**6.87E-11**	**186,521**
EST 14	***FGF5***	rs1458038	4	81,164,723	T/C	0.3	**SBP** & DBP	**0.659**	**0.065**	**5.36E-24**	**188,136**	**0.392**	**0.04**	**7.36E-23**	**188,088**
EST 15	***ARHGAP24***	rs17010957	4	86,719,165	T/C	0.857	**SBP**	**-0.498**	**0.082**	**1.51E-09**	**196,325**	-0.173	0.051	6.63E-04	196,292
EST 16	***SLC39A8***	rs13107325	4	103,188,709	T/C	0.07	SBP & **DBP**	**-0.837**	**0.127**	**4.69E-11**	**175,292**	**-0.602**	**0.078**	**1.63E-14**	**175,372**
EST 17	***GUCY1A3-GUCY1B3***	rs4691707	4	156,441,314	A/G	0.652	**SBP**	**-0.349**	**0.06**	**7.10E-09**	**198,246**	-0.163	0.037	1.08E-05	198,226
EST 18	***NPR3-C5orf23***	rs12656497	5	32,831,939	T/C	0.403	**SBP** & DBP	**-0.487**	**0.06**	**3.85E-16**	**194,831**	**-0.228**	**0.037**	**4.73E-10**	**194,829**
EST 19	***EBF1***	rs11953630	5	157,845,402	T/C	0.366	**SBP** & DBP	**-0.38**	**0.065**	**3.91E-09**	**167,698**	**-0.23**	**0.04**	**8.07E-09**	**167,708**
EST 20	***HFE***	rs1799945*	6	26,091,179	C/G	0.857	SBP & **DBP**	**-0.598**	**0.086**	**3.28E-12**	**185,306**	**-0.43**	**0.053**	**3.10E-16**	**185,273**
EST 21	***BAT2-BAT5***	rs2187668	6	32,605,884	T/C	0.126	**DBP**	-0.291	0.092	1.60E-03	189,806	**-0.372**	**0.057**	**4.31E-11**	**189,810**
EST 22	***ZNF318-ABCC10***	rs6919440	6	43,352,898	A/G	0.57	**SBP**	**-0.337**	**0.058**	**4.92E-09**	**200,733**	-0.125	0.035	4.25E-04	200,730
EST 23	***RSPO3***	rs1361831	6	127,181,089	T/C	0.541	**SBP** & DBP	**-0.482**	**0.058**	**7.38E-17**	**197,027**	**-0.271**	**0.036**	**2.34E-14**	**197,012**
EST 24	***PLEKHG1***	rs17080093	6	150,997,440	T/C	0.075	**DBP**	-0.564	0.111	3.83E-07	194,728	**-0.411**	**0.068**	**1.71E-09**	**194,734**
EST 25	***HOTTIP-EVX***	rs3735533	7	27,245,893	T/C	0.081	**SBP** & DBP	**-0.798**	**0.106**	**6.48E-14**	**197,881**	**-0.445**	**0.065**	**1.09E-11**	**197,880**
EST 26	***PIK3CG***	rs12705390	7	106,410,777	A/G	0.227	**SBP**	**0.619**	**0.069**	**2.69E-19**	**198,297**	0.059	0.042	1.63E-01	198,290
EST 27	***BLK-GATA4***	rs2898290	8	11,433,909	T/C	0.491	**SBP**	**0.377**	**0.058**	**8.85E-11**	**197,759**	0.167	0.036	3.17E-06	197,726
EST 28	***CACNB2***	rs12243859	10	18,740,632	T/C	0.326	SBP & **DBP**	**-0.402**	**0.061**	**6.13E-11**	**199,136**	**-0.335**	**0.038**	**8.11E-19**	**199,124**
EST 29	***C10orf107***	rs7076398	10	63,533,663	A/T	0.188	SBP & **DBP**	**-0.563**	**0.076**	**1.72E-13**	**187,013**	**-0.409**	**0.047**	**2.55E-18**	**187,024**
EST 30	***SYNPO2L***	rs12247028	10	75,410,052	A/G	0.611	**SBP**	**-0.364**	**0.063**	**8.16E-09**	**180,194**	-0.159	0.039	3.89E-05	180,094
EST 31	***PLCE1***	rs932764*	10	95,895,940	A/G	0.554	**SBP** & DBP	**-0.495**	**0.059**	**6.88E-17**	**195,577**	**-0.224**	**0.036**	**6.28E-10**	**195,547**
EST 32	***CYP17A1-NT5C2***	rs943037	10	104,835,919	T/C	0.087	**SBP** & DBP	**-1.133**	**0.105**	**2.35E-27**	**193,818**	**-0.482**	**0.064**	**4.48E-14**	**193,799**
EST 33	***ADRB1***	rs740746	10	115,792,787	A/G	0.73	SBP & **DBP**	**0.486**	**0.067**	**4.59E-13**	**184,835**	**0.32**	**0.041**	**8.63E-15**	**184,868**
EST 34	***LSP1-TNNT3***	rs592373	11	1,890,990	A/G	0.64	**SBP** & DBP	**0.484**	**0.063**	**2.02E-14**	**177,149**	**0.282**	**0.039**	**3.61E-13**	**177,134**
EST 35	***ADM***	rs1450271	11	10,356,115	T/C	0.468	**SBP** & DBP	**0.413**	**0.059**	**3.40E-12**	**191,246**	**0.199**	**0.036**	**4.11E-08**	**191,221**
EST 36	***PLEKHA7***	rs1156725	11	16,307,700	T/C	0.804	SBP & **DBP**	**-0.447**	**0.072**	**5.65E-10**	**200,889**	**-0.292**	**0.044**	**3.67E-11**	**200,899**
EST 37	***SIPA1***	rs3741378*	11	65,408,937	T/C	0.137	**SBP**	**-0.486**	**0.084**	**8.04E-09**	**194,563**	-0.183	0.052	4.17E-04	194,551
EST 38	***FLJ32810-TMEM133***	rs633185	11	100,593,538	C/G	0.715	**SBP** & DBP	**0.522**	**0.067**	**6.97E-15**	**183,845**	**0.288**	**0.041**	**2.38E-12**	**183,825**
EST 39	***PDE3A***	rs3752728	12	20,192,972	A/G	0.737	**DBP**	0.331	0.066	4.32E-07	200,440	**0.319**	**0.04**	**2.35E-15**	**200,408**
EST 40	***ATP2B1***	rs11105354	12	90,026,523	A/G	0.84	**SBP** & DBP	**0.909**	**0.081**	**3.88E-29**	**195,206**	**0.459**	**0.05**	**2.61E-20**	**195,195**
EST 41	***SH2B3***	rs3184504*	12	111,884,608	T/C	0.475	SBP & **DBP**	**0.498**	**0.062**	**9.97E-16**	**177,067**	**0.362**	**0.038**	**1.28E-21**	**177,122**
EST 42	***TBX5-TBX3***	rs2891546	12	115,552,499	A/G	0.11	**DBP**	-0.529	0.1	1.36E-07	172,012	**-0.38**	**0.061**	**4.71E-10**	**171,980**
EST 43	***CYP1A1-ULK3***	rs936226	15	75,069,282	T/C	0.722	SBP & **DBP**	**-0.549**	**0.067**	**3.06E-16**	**187,238**	**-0.363**	**0.041**	**1.03E-18**	**187,221**
EST 44	***FURIN-FES***	rs2521501	15	91,437,388	A/T	0.684	**SBP** & DBP	**-0.639**	**0.069**	**3.35E-20**	**164,272**	**-0.358**	**0.042**	**1.85E-17**	**164,255**
EST 45	***PLCD3***	rs7213273	17	43,155,914	A/G	0.658	**SBP**	**-0.413**	**0.066**	**4.71E-10**	**164,795**	**-0.185**	0.041	7.23E-06	164,788
EST 46	***GOSR2***	rs17608766	17	45,013,271	T/C	0.854	**SBP**	**-0.658**	**0.083**	**2.27E-15**	**188,895**	-0.218	0.051	1.95E-05	188,928
EST 47	***ZNF652***	rs12940887	17	47,402,807	T/C	0.38	**DBP**	0.321	0.06	7.06E-08	192,546	**0.261**	**0.037**	**1.07E-12**	**192,524**
EST 48	***JAG1***	rs1327235	20	10,969,030	A/G	0.542	SBP & **DBP**	**-0.395**	**0.059**	**2.23E-11**	**192,680**	**-0.308**	**0.036**	**1.78E-17**	**192,659**
EST 49	***GNAS-EDN3***	rs6026748	20	57,745,815	A/G	**0.125**	SBP & **DBP**	**0.867**	**0.089**	**3.15E-22**	**192,338**	**0.552**	**0.055**	**4.86E-24**	**192,327**

Table 2. BP risk score effects on disease outcomes.

Phenotype	Var. type (cont./ dic.)	Eth.	Consort.	Total N or no. ca/co	Total #SNPs	SBP_score					DBP_score				
						effect (all)	*P* value (all)	het. *P* value (all)	*P* value (p)	# SNPs rem.	effect (all)	*P* value (all)	het. *P* value (all)	*P* value (p)	# SNPs rem.
HEART															
CAD	dich.	EUR SAS	CARDIoGRAMplusC4D	63,746 /130,681	61	1.042	**1.72E-44**	1.75E-25	**4.08E-32**	10	1.069	**1.19E-42**	6.63E-27	**2.2E-38**	10
heart failure	dich.	EUR	CHARGE	2,526 /18,400	66	1.021	2.77E-02	1.63E-01	2.77E-02	0	1.035	2.31E-02	1.70E-01	2.31E-02	0
LV mass	cont.	EUR	CHARGE	11,273	66	0.480	**6.43E-04**	3.58E-01	**6.43E-04**	0	0.754	**1.23E-03**	3.21E-01	**1.23E-03**	0
LV wall thickness	cont.	EUR	CHARGE	11,311	66	0.004	**4.45E-06**	5.83E-02	**4.45E-06**	0	0.007	**3.19E-06**	6.40E-02	**3.19E-06**	0
KIDNEY															
CKD	dich.	EUR	CHARGE	6,271 /68,083	65	1.010	1.37E-01	1.77E-03	2.65E-01	1	1.008	4.49E-01	1.25E-03	7.69E-01	1
eGFR (based on cr)	cont.	EUR	CHARGE	74,354	65	0.000	7.07E-01	3.12E-05	3.22E-01	2	0.000	9.41E-01	3.02E-05	9.65E-01	2
eGFR (based on cystatin)	cont.	EUR	CHARGE	74,354	65	0.001	9.05E-02	9.28E-06	4.11E-01	1	0.001	3.30E-01	5.64E-06	6.9E-01	1
creatinine	cont.	EUR	KidneyGEN	23,812	66	0.000	9.42E-01	6.31E-03	9.42E-01	0	0.000	4.11E-01	7.16E-03	4.11E-01	0
microalbuminuria	dich.	EUR	CHARGE	2,499 /29,081	65	0.011	2.10E-01	4.79E-02	2.1E-01	0	0.023	1.02E-01	5.66E-02	1.02E-02	0
urinary albumin/cr ratio	cont.	EUR	CHARGE	31,580	65	0.009	**2.52E-03**	3.02E-04	0.53E-03	1	0.015	**2.40E-03**	3.08E-04	8.31E-03	1
STROKE															
stroke, all subtypes	dich.	EUR	CHARGE	1,544 /18,058	66	0.056	**6.11E-06**	8.26E-02	**6.11E-06**	0	0.085	**3.79E-05**	4.98E-02	**3.79E-05**	0
stroke, ischemic subtype	dich.	EUR	CHARGE	1,164 /18,438	66	0.067	**3.33E-06**	1.75E-01	**3.33E-06**	0	0.096	**5.63E-05**	8.82E-02	**5.63E-05**	0
stroke, ischemic subtype	dich.	EUR	MetaStroke	11,012 /40,824	66	0.036	**1.69E-10**	4.72E-02	**1.69E-10**	0	0.056	**1.29E-09**	2.51E-02	**1.29E-09**	0
VASCULATURE															
cIMT	cont.	EUR	CHARGE	27,610	66	0.004	**4.80E-15**	5.06E-08	**7.32E-10**	4	0.005	**4.15E-11**	3.84E-10	**6.2E-07**	5
EYE															
mild retinop.	dich.	EUR	CHARGE	1,122 /18,289	66	1.021	1.37E-01	6.01E-03	1.37E-01	0	1.046	5.78E-02	7.81E-03	5.78E-02	0
central retinal artery caliber	cont.	EUR	CHARGE	18,576	66	0.343	**3.29E-14**	2.56E-06	**2.06E-13**	2	0.570	**3.61E-14**	2.44E-06	**7.05E-13**	3
mild retinop.	dich.	EAS	SEED	289 /5,419	66	1.033	2.55E-01	2.42E-01	2.55E-01	0	1.087	8.55E-02	2.87E-01	8.55E-02	0
central retinal artery caliber	cont.	EAS	SEED	6,976	63	0.320	**1.39E-04**	9.07E-01	**1.39E-04**	0	0.533	**2.19E-04**	8.91E-01	**2.19E-04**	0

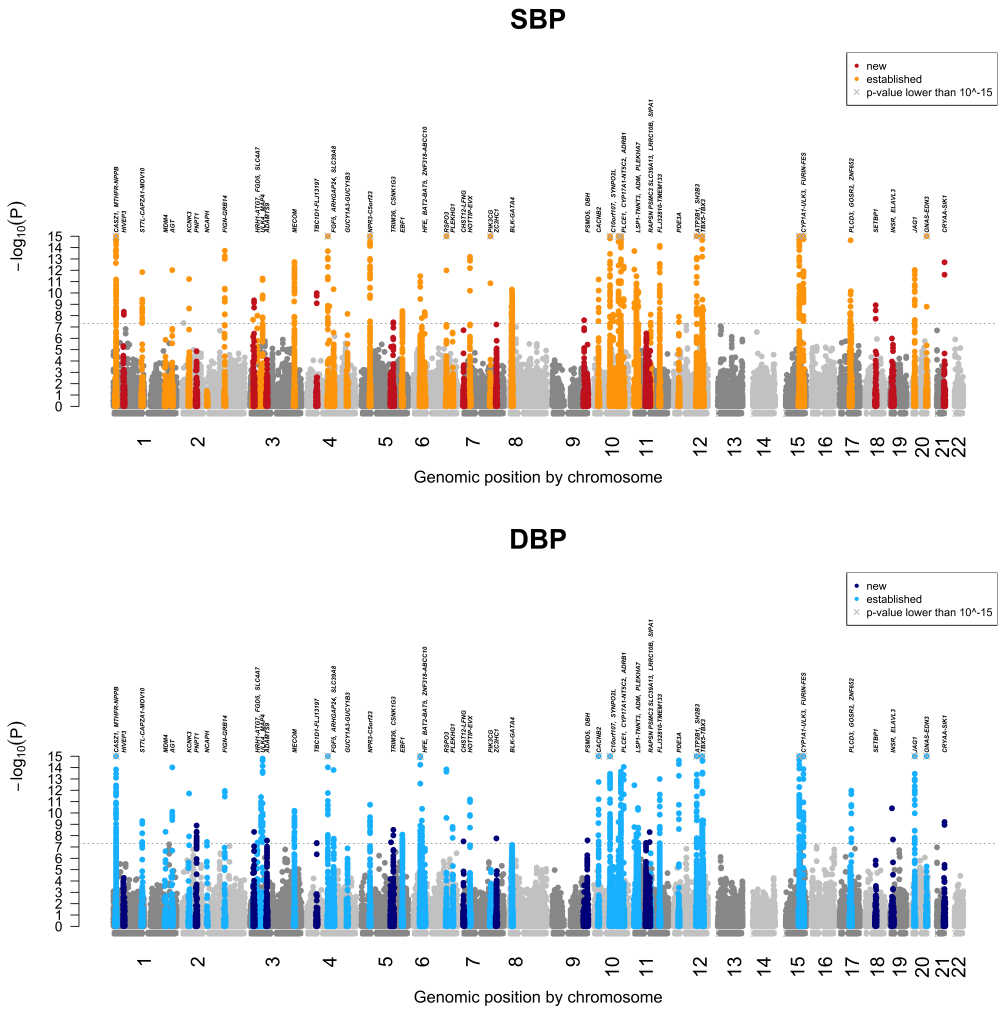

Figure 1. Manhattan plots for SBP and DBP from the stage 4 Cardio-MetaboChip-wide meta-analysis. P values (expressed as $-log_{10}P$) are plotted by physical genomic position labeled by chromosome. SNPs in new loci (3.5MB window around the index SNP), identified in this study, are labeled in dark red (SBP) or dark blue (DBP); SNPs in previously known loci are labeled in orange (SBP) or light blue (DBP). The locus names are indicated. The grey crosses indicate genomic positions at which the y-axis was truncated (SNPs with $P < 10^{-15}$).

	17 new loci	49 established loci	all 66 loci
Minor allele frequency, (mean, range)	32.1% [5%-50%]	28.9% [7%-49%]	29.8% [5%-50%]
Effect size SBP [mmHg], (range, mean)	0.09-0.59 0.34	0.07-1.13 0.5	0.07-1.13 0.46
Effect size DBP [mmHg] (range, mean)	0.1-0.46 0.23	0.06-0.6 0.3	0.06-0.6 0.28
Variance explained SBP	0.52%	2.95%	3.46%
Variance explained DBP	0.58%	2.78%	3.36%
Previously known for BP	5/20	-	-

Figure 2. Overview of novel and known BP variant properties. Key characteristics of the novel and established BP loci are shown. MAF and effect size estimates are derived from the Cardio-MetaboChip data. Variance explained estimates are estimated from one large study (**Supplementary Note**). Novel loci are classified as previously unknown to be linked to BP by a systematic PubMed review of all genes in a 200kb window (**Supplementary Note**).

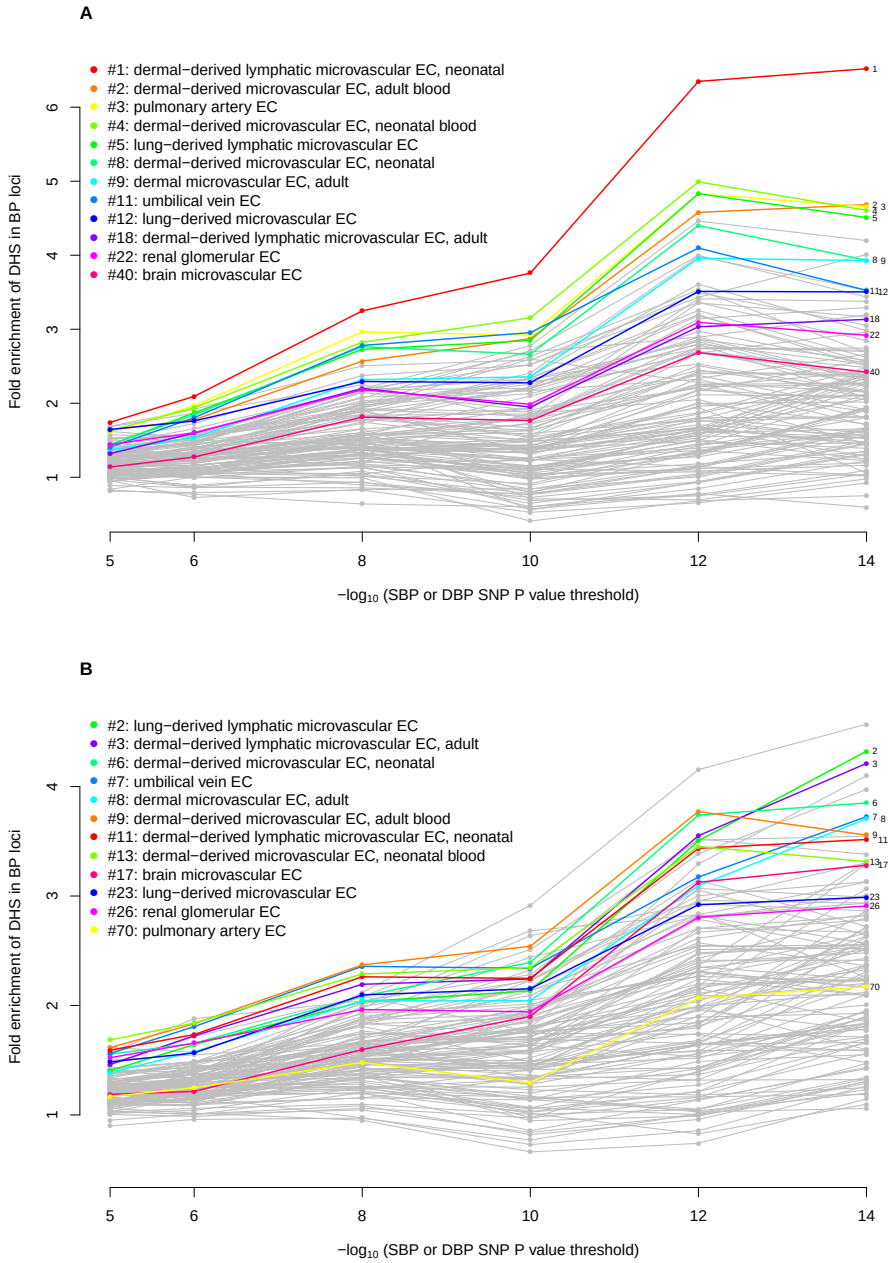

Figure 3. Enrichment of DNAse hypersensitive sites among BP loci in different cell-types. Enrichment analyses of SBP or DBP associated loci according to discovery *P* value using narrow peaks (panel A) or broad peaks (panel B). SNPs were selected according to different *P* value cutoffs (x-axis) and a fold enrichment of overlap with DNAse hypersensitive sites compared to unrelated GWAS SNPs was calculated (y-axis) (see **Supplementary Note**). The 12 endothelial cell-lines are indicated in color and for each endothelial cell-type the rank using the 10^{-14} *P* value cutoff is indicated. EC denotes endothelial cells.

AUTHORS

Georg B. Ehret[1,2,3*], Teresa Ferreira[4*], Daniel I. Chasman[5,6], Anne U. Jackson[7], Ellen M. Schmidt[8], Toby Johnson[9,10], Gudmar Thorleifsson[11], Jian'an Luan[12], Lousie A. Donnelly[13], Stavroula Kanoni[14], Ann-Kristin Petersen[15], Vasyl Pihur[1], Rona J. Strawbridge[16,17], Dmitry Shungin[18,19,20], Maria F. Hughes[21], Osorio Meirelles[22], Marika Kaakinen[23], Nabila Bouatia-Naji[24,25], Kati Kristiansson[26,27], Sonia Shah[28], Marcus E. Kleber[29], Xiuqing Guo[30], Leo-Pekka Lyytikäinen[31,32], Cristiano Fava[33,34], Niclas Eriksson[35], Ilja M. Nolte[36], Patrik K. Magnusson[37], Elias L. Salfati[38], Loukianos S. Rallidis[39], Elizabeth Theusch[40], Andrew J.P. Smith[41], Lasse Folkersen[16], Kate Witkowska[9,42], Tune H. Pers[43,44,268,269], Roby Joehanes[45], Stuart K. Kim[46], Lazaros Lataniotis[14], Rick Jansen[47], Andrew D. Johnson[45,48], Helen Warren[9,42], Young Jin Kim[49], Wei Zhao[50], Ying Wu[51], Bamidele O. Tayo[52], Murielle Bochud[3], Devin Absher[53], Linda S. Adair[54], Najaf Amin[55], Dan E. Arking[1], Tomas Axelsson[56], Damiano Baldassarre[57,58], Beverley Balkau[59], Stefania Bandinelli[60], Michael R. Barnes[14,42], Ines Barroso[61,62], Stephen Bevan[63], Joshua C. Bis[64], Gyda Bjornsdottir[11], Michael Boehnke[7], Eric Boerwinkle[65], Lori L. Bonnycastle[66], Dorret I. Boomsma[67], Stefan R. Bornstein[68], Morris J. Brown[69], Michel Burnier[70], Claudia P. Cabrera[9,42], John C. Chambers[71,72,73], I-Shou Chang[74], CHARGE-EchoGen consortium, CHARGE-HF consortium CHARGE-HF consortium, Ching-Yu Cheng[75,76,77], Peter S. Chines[66], Ren-Hua Chung[78], Francis S. Collins[66], John M. Connell[79], Angela Döring[80,81], Jean Dallongeville[82], John Danesh[83], Ulf de Faire[84], Graciela Delgado[29], Vaidya Dhananjay[85], Anna F. Dominiczak[86], Alex S.F. Doney[13], Fotios Drenos[41], Sarah Edkins[61], John D. Eicher[45,48], Roberto Elosua[87], Stefan Enroth[88], Jeanette Erdmann[89,90], Per Eriksson[16], Tonu Esko[91,92,93], Evangelos Evangelou[71,94], Alun Evans[21], Tove Fall[95], Martin Farrall[4,96], Janine F. Felix[97], Jean Ferrières[98], Luigi Ferrucci[99], Myriam Fornage[100], Terrence Forrester[101], Nora Franceschini[102], Oscar H. Franco Duran[97], Anders Franco-Cereceda[103], Ross M. Fraser[104,105], Santhi K. Ganesh[106], He Gao[71], Karl Gertow[16,17], Francesco Gianfagna[107,108], Bruna Gigante[84], Franco Giulianini[5], Anuj Goel[4,96], Alison H. Goodall[109,110], Mark O. Goodarzi[111], Mathias Gorski[112,113], Jürgen Gräßler[114], Christopher Groves[115], Vilmundur Gudnason[116,117], Ulf Gyllensten[88], Göran Hallmans[18], Anna-Liisa Hartikainen[118,119], Maija Hassinen[120], Aki S. Havulinna[26], Caroline Hayward[121], Serge Hercberg[122], Karl-Heinz Herzig[123,124,125], Andrew A. Hicks[126], Aroon Hingorani[28], Joel N. Hirschhorn[43,44,127], Albert Hofman[97], Jostein Holmen[128], Oddgeir Lingaas Holmen[128,129], Jouke-Jan Hottenga[67], Phil Howard[41], Chao A. Hsiung[78], Steven C. Hunt[130,131], M. Arfan Ikram[97,132,133], Thomas Illig[134,135,136], Carlos Iribarren[137], Richard A. Jensen[64,138], Mika Kähönen[139,140], Hyun Kang[7], Sekar Kathiresan[141,142,143,144], Brendan J. Keating[145,146], Kay-Tee Khaw[147], Yun Kyoung Kim[49], Eric Kim[148], Mika Kivimaki[28], Norman Klopp[134,135], Genovefa Kolovou[149], Pirjo Komulainen[120], Jaspal S. Kooner[150,72,73], Gulum Kosova[151,141,152], Ronald M. Krauss[153], Diana Kuh[154], Zoltan Kutalik[155,156], Johanna Kuusisto[157], Kirsti Kvaløy[128], Timo A Lakka[158,120,159], Nanette R. Lee[160], I-Te

Lee[161,162], Wen-Jane Lee[163], Daniel Levy[45,164], Xiaohui Li[30], Kae-Woei Liang[165,166], Honghuang Lin[167,45], Li Lin[2], Jaana Lindström[26], Stéphane Lobbens[168,169,170], Satu Männistö[26], Gabriele Müller[171], Martina Müller-Nurasyid[15,172,173], François Mach[2], Hugh Markus[63], Eirini Marouli[14,174], Mark I. McCarthy[115], Colin A. McKenzie[101], Pierre Meneton[175], Cristina Menni[176], Andres Metspalu[91], Vladan Mijatovic[177], Leena Moilanen[178,179], May E. Montasser[180], Andrew D. Morris[13], Alanna C. Morrison[181], Antonella Mulas[182], Ramaiah Nagaraja[22], Narisu Narisu[66], Kjell Nikus[183,184], Christopher J. O'Donnell[185,45,186], Paul O'Reilly[187], Ken K. Ong[12], Fred Paccaud[3], Cameron D. Palmer[188,189], Afshin Parsa[180], Nancy L. Pedersen[37], Brenda W. Penninx[190,191,192], Markus Perola[26,27,193], Annette Peters[81], Neil Poulter[194], Peter P. Pramstaller[126,195,196], Bruce M. Psaty[64,197,198,199], Thomas Quertermous[38], Dabeeru C. Rao[200], Asif Rasheed[201], N William N.W.R. Rayner[202,203,61], Frida Renström[19,204,18], Rainer Rettig[205], Kenneth M. Rice[206], Robert Roberts[207,208], Lynda M. Rose[5], Jacques Rossouw[209], Nilesh J. Samani[109,210], Serena Sanna[182], Jouko Saramies[211], Heribert Schunkert[212,213,214], Sylvain Sebert[215,124,159], Wayne H.-H. Sheu[216,162,217], Young-Ah Shin[49], Xueling Sim[7,218], Johannes H. Smit[190], Albert V. Smith[116,117], Maria X. Sosa[1], Tim D. Spector[176], Alena Stančáková[219], Alice Stanton[220], Kathleen E. Stirrups[14,221], Heather M. Stringham[7], Johan Sundstrom[56], Amy J. Swift[66], Ann-Christine Syvänen[56], E-Shyong Tai[222,76,218], Toshiko Tanaka[99], Kirill V. Tarasov[223], Alexander Teumer[224], Unnur Thorsteinsdottir[11,225], Martin D. Tobin[226], Elena Tremoli[57,58], Andre G. Uitterlinden[97,227], Matti Uusitupa[228,229], Ahmad Vaez[36], Cornelia M. van Duijn[97,230], Erik P.A. van Iperen[231,232], Ramachandran S. Vasan[45,233], Germaine C. Verwoert[97], Jarmo Virtamo[26], Veronique Vitart[121], Benjamin F. Voight[234,235], Peter Vollenweider[236], Aline Wagner[237], Louise V. Wain[226], Nicholas J. Wareham[12], Hugh Watkins[4,96], Alan B. Weder[238], Wellcome Trust Case Control Consortium, Harm-Jan Westra[239], Rainford Wilks[240], Tom Wilsgaard[241,242], James F. Wilson[104,121], Tien Y. Wong[75,76,77], Tsun-Po Yang[14,243], Jie Yao[244], Loic Yengo[168,169,170], Weihua Zhang[71,72], Jing Hua Zhao[12], Xiaofeng Zhu[245], Pascal Bovet[246,3], Richard S. Cooper[52], Karen L. Mohlke[51], Danish Saleheen[247,201], Jong-Young Lee[49], Paul Elliott[71,248], Hinco J. Gierman[46,249], Cristen J. Willer[8,250,251], Lude Franke[252], G Kees Hovingh[253], Kent D. Taylor[30], George Dedoussis[174], Peter Sever[194], Andrew Wong[154], Lars Lind[56], Themistocles L. Assimes[38], Inger Njølstad[241,242], Peter EH. Schwarz[68], Claudia Langenberg[12], Harold Snieder[36], Mark J. Caulfield[9,42], Olle Melander[33], Markku Laakso[157], Juha Saltevo[254], Rainer Rauramaa[120,159], Jaakko Tuomilehto[26,255,256,257], Erik Ingelsson[95,4], Terho Lehtimäki[31,32], Kristian Hveem[128], Walter Palmas[258], Winfried März[259,260], Meena Kumari[28], Veikko Salomaa[26], Yii-Der I. Chen[30], Jerome I. Rotter[30], Philippe Froguel[168,169,170,23], Marjo-Riitta Jarvelin[215,124,261,262], Edward G. Lakatta[223], Kari Kuulasmaa[26], Paul W. Franks[19,204,18], Anders Hamsten[16,17], H.-Erich Wichmann[80,263,264], Colin N.A. Palmer[13], Kari Stefansson[11,225], Paul M Ridker[5,6], Ruth J.F. Loos[12,265], Aravinda Chakravarti[1], Panos Deloukas[14,266], Andrew P. Morris[267,4*#], Christopher Newton-

Cheh[141,189,152*#$], Patricia B. Munroe[9,42*#$]

[*] These authors contributed equally to this work.
[#] These authors jointly supervised this work.
[$] Corresponding authors: Christopher Newton-Cheh (cnewtoncheh@mgh.harvard.edu) and Patricia B. Munroe (p.b.munroe@qmul.ac.uk).

AUTHOR AFFILIATIONS

1. Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
2. Cardiology, Department of Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland
3. Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Route de la Corniche 10, 1010 Lausanne, Switzerland
4. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK
5. Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave. East, Boston, MA 02215, USA
6. Harvard Medical School, Boston, MA 02115, USA
7. Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI 48109, USA
8. Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA
9. Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London, EC1M 6BQ, UK
10. GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, UK
11. deCODE Genetics/Amgen, Inc., Reykjavik, Iceland
12. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK
13. Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK
14. William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
15. Institute of Genetic Epidemiology, Helmholtz Zentrum München, Neuherberg 85764, Germany
16. Atherosclerosis Research Unit, Center for Molecular Medicine L8:03, Department of Medicine, Karolinska Institutet, 171 76 Stockholm, Sweden
17. Center for Molecular Medicine, Karolinska University Hospital Solna, Stockholm, Sweden
18. Department of Public Health and Clinical Medicine, Ume University, Sweden
19. Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Skåne University Hospital Malmö, SE-205 02 Malmö, Sweden
20. Department of Odontology, Ume University, Sweden
21. Centre of Excellence for Public Health, Queens University Belfast, Grosvenor Road, Belfast BT126JP, UK
22. Laboratory of Genetics, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA
23. Department of Genomics of Common Disease, School of Public Health, Imperial College London, Hammersmith Hospital, London, UK
24. INSERM UMR970, Paris Cardiovascular Research Center PARCC, 56 rue Leblanc, 75015 Paris, France
25. University Paris-Descartes, Sorbonne Paris Cité, 12 rue de l'Ecole de medicine F-75006 Paris, France
26. National Institute for Health and Welfare, FI-00271 Helsinki, Finland
27. Institute for Molecular Medicine Finland FIMM, University of Helsinki, 00290 Helsinki, Finland
28. Genetic Epidemiology Group, Dept. Epidemiology and Public Health, UCL, London, WC1E 6BT, UK
29. Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany
30. Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA

31. Department of Clinical Chemistry, Fimlab Laboratories, Tampere 33520, Finland
32. Department of Clinical Chemistry, University of Tampere School of Medicine, Tampere 33014, Finland
33. University of Lund, Dept Internal Medicine, Malmo, SE 20502, Sweden
34. University of Verona, Dept of Internal Medicine, Verona, Italy 37134
35. Uppsala University, Uppsala Clinical Research Center, SE-75185 Uppsala, Sweden
36. Department of Epidemiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
37. Dept of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden
38. Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
39. Second Department of Cardiology, Attikon Hospital, School of Medicine, University of Athens, Athens, Greece
40. Children's Hospital Oakland Research Institute, Oakland, CA 94609, USA
41. Department of Cardiovascular Genetics, Institute of Cardiovascular Sciences, University College London, London WC1E 6JF, UK
42. NIHR Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, EC1M 6BQ, UK
43. Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA 02115, USA
44. Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, 02142, USA
45. National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA 01702, USA
46. Dept. Dev. Bio. And Genetics, Stanford University Medical Center, Stanford, CA 94305, USA
47. Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
48. National Heart, Lung and Blood Institute, Cardiovascular Epidemiology and Human Genomics Branch, Bethesda, MD 20814, USA
49. Center for Genome Science, National Institute of Health, Osong Health Technology Administration Complex, Chungcheongbuk-do, Republic of Korea
50. Division of Translational Medicine and Human Genetics, Department of Medicine, University of Pennyslvania, USA
51. Department of Genetics, University of North Carolina, Chapel Hill, NC 27599, USA
52. Department of Preventive Medicine and Epidemiology, Loyola University Chicago Stritch School of Medicine, Maywood, IL, 60153, USA
53. HudsonAlpha Institute for Biotechnology, Huntsville, AL 35086, USA
54. Department of Nutrition, University of North Carolina, Chapel Hill, NC 27599, USA
55. Genetic Epidemiology Unit, Department of Epidemiology, Erasmus MC, Rotterdam, 3015CN, The Netherlands
56. Uppsala University, Department of Medical Sciences, SE-75185 Uppsala, Sweden
57. Dipartimento di Scienze Farmacologiche e Biomolecolari, Università di Milano, Milan, Italy
58. Centro Cardiologico Monzino, IRCCS, Milan, Italy
59. INSERM Centre for Research in Epidemiology and Population Health, U1018, Villejuif, France University Paris-Sud, URMS 1018, Villejuif, France
60. Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy
61. Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, CB10 1SA, Hinxton, UK
62. University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Level 4, Institute of Metabolic Science Box 289 Addenbrookes Hospital Cambridge CB2 OQQ, UK

63. Neurology Unit, University of Cambridge, R3, Box 83, Cambridge Biomedical Campus, Cambridge, Cb2 0QQ, UK
64. Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA 98101, USA
65. Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, 1200 Pressler St., Suite 453E, Houston, TX 77030, USA
66. Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD 20892, USA
67. Department of Biological Psychology, VU University, Amsterdam, The Netherlands
68. Dept of Medicine III, University of Dresden, Medical Faculty Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany
69. Clinical Pharmacology Unit, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK
70. Nephrology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Bugnon 17, 1005 Lausanne, Switzerland
71. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK
72. Department of Cardiology, Ealing Hospital NHS Trust, Uxbridge Road, Southall, Middlesex UB1 3EU, UK
73. Imperial College Healthcare NHS Trust, London, UK
74. National Institute of Cancer Research, National Health Research Institutes. 35 Keyan Rd., Zhunan Town, Miaoli County 350, Taiwan
75. Singapore Eye Research Institute, Singapore National Eye Centre, Singapore 168751, Singapore
76. Duke-NUS Graduate Medical School Singapore, Singapore 169857, Singapore
77. Department of Ophthalmology, National University of Singapore and National University Health System, Singapore 119228
78. Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes. 35 Keyan Rd., Zhunan Town, Miaoli County 350, Taiwan
79. University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK
80. Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg 85764, Germany
81. Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg 85764, Germany
82. UMR744 Inserm-Lille2-Institut Pasteur Lille, France
83. Department of Public Health and Primary Care, University of Cambridge, UK
84. Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
85. Johns Hopkins Medical Institutions, 1830 East Monument St., Baltimore, MD 21287, USA
86. BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow, G12 8QT, UK
87. Cardiovascular Epidemiology and Genetics. IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain
88. Dept of Immunology, Genetics, Pathology, Science for Life Laboratory, University of Uppsala, Box 815, Biomerical center, 751 08 Uppsala, Sweden
89. Institut für Integrative und Experimentelle Genomik, Universiät zu Lübeck, RatzeburgerAllee 160, 23538 Lübeck, Germany
90. Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), partner site Hamburg, Kiel, Lübeck, Universität zu Lübeck, Lübeck, Germany
91. Estonian Genome Center, University of Tartu, Tartu, 51010, Estonia
92. Divisions of Endocrinology/Children's Hospital, Boston, MA 02115, USA

93. Broad Institute of MIT and Harvard, Cambridge, MA, 02142, USA
94. Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, 45110, Greece
95. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
96. Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, OX3 9DU, UK
97. Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, P.O.Box 2040, 3000 CA Rotterdam, The Netherlands
98. Toulouse University School of Medicine, Rangueil University Hospital, INSERM UMR1027, Toulouse, France
99. Translational Gerontology Branch, National Institute on Aging, Baltimore MD, USA
100. Institute of Molecular Medicine, University of Texas Health Science Center at Houston, TX, USA
101. Tropical Metabolism Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston 7, Jamaica
102. Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27599, USA
103. Cardiothoracic Surgery Unit, Department of Molecular Medicine and Surgery, Karolinska Institutet, 171 76 Stockholm, Sweden
104. Institute for Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland
105. Synpromics Ltd, 9 Bioquarter, Little France Road, Edinburgh, EH16 4UX, Scotland
106. University of Michigan Medical School, 7220 MSRB III, Ann Arbor MI 48109, USA
107. EPIMED Research Centre - Epidemiology and Preventive Medicine, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy
108. Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo NEUROMED, 86077 Pozzilli, Italy
109. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester LE3 9QP, UK
110. National Institute for Health Research Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester LE3 9QP, UK
111. Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA
112. Department of Genetic Epidemiology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
113. Department of Nephrology, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
114. Department of Medicine III, Division Pathobiochemistry, Technische Universität Dresden, Dresden, Germany
115. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford,UK
116. Icelandic Heart Association, Kopavogur, Iceland
117. Faculty of medicine, University of Iceland, Reykjavik, Iceland
118. Institute of Clinical Medicine/Obstetrics and Gynaecology, University of Oulu, Oulu, Finland
119. Medical Research Center, Oulu University Hospital, Oulu, Finland
120. Kuopio Research Institute of Exercise Medicine, Kuopio, Finland
121. Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU Scotland, UK
122. UREN, INSERM U557, INRA U1125, CNAM, SMBH, Sorbonne Paris Cité, Université Paris 13, Bobigny, France

123. Institute of Biomedicine, University of Oulu, Medical Research Center Oulu and Oulu University Hospital, Finland
124. Biocenter Oulu, P.O.Box 5000, Aapistie 5A, FI-90014 University of Oulu, Finland
125. Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland
126. Center for Biomedicine, European Academy Bozen/Bolzano (EURAC), Bolzano, 39100, Italy - affiliated institute of the University of Lübeck, Germany
127. Department of Genetics, Harvard Medical School, Boston, 02115, USA
128. HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, 7600 Levanger, Norway
129. St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway
130. Cardiovascular Genetics Division, University of Utah School of Medicine, Salt Lake City, Utah, USA
131. Department of Genetic Medicine, Weill Cornell Medical College Qatar, Doha, Qatar
132. Department of Radiology, Erasmus MC, The Netherlands
133. Department of Neurology, Erasmus MC, University Medical Center Rotterdam, P.O.Box 2040, 3000 CA Rotterdam, The Netherlands
134. Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg 85764, Germany
135. Hannover Unified Biobank, Hannover Medical School, Hannover 30625, Germany
136. Hannover Medical School, Institute for Human Genetics, Carl-Neuberg-Strasse 1, 30625 Hanover, Germany
137. Kaiser Permanente, Division of Research, Oakland, CA 94612, USA
138. Department of Medicine, University of Washington, Seattle, Washington 98101, USA
139. Department of Clinical Physiology, Tampere University Hospital, Tampere 33521, Finland
140. Department of Clinical Physiology, University of Tampere School of Medicine, Tampere 33014, Finland
141. Center for Human Genetic Research, Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA 02114, USA
142. Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA
143. Department of Medicine, Harvard Medical School, Boston, MA, USA
144. Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA
145. Division of Transplantation, Department of Surgery, University of Pennsylvania, PA 19104 USA
146. Department of Pediatrics, University of Pennsylvania, Philadelphia, PA, USA
147. Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 2SR, UK
148. Institute for Translational Genomics and Population Sciences, Department of Pediatrics, LABioMed at Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA
149. 1st Cardiology Department, Onassis Cardiac Surgery Center 356, Sygrou Ave, Athens, Greece
150. National Heart and Lung Institute, Imperial College London, Hammersmith Hospital Campus, Ducane Road, London W12 0NN, UK
151. Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA 02114, USA
152. Broad Institute of Harvard and MIT, Cambridge, MA 02139 USA
153. Department of Medicine, Children's Hospital Oakland Research Institute, Oakland, CA 94609, USA
154. MRC Unit for Lifelong Health and Ageing at UCL, London, WC1B 5JU, UK
155. Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland
156. Swiss Institute of Bioinformatics, Lausanne, Switzerland

157. Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland
158. Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio Campus, Finland
159. Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland
160. Office of Population Studies Foundation Inc. and Department of Anthropology, Sociology, and History, University of San Carlos, Talamban, Cebu City, 6000, Philippines
161. Division of Endocrine and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung 40705, Taiwan
162. School of Medicine, National Yang-Ming University, Taipei, Taiwan
163. Department of Medical Research, Taichung Veterans General Hospital, Taichung 407, Taiwan
164. Population Sciences Branch, National Heart Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA
165. Cardiovascular Center, Taichung Veterans General Hospital, Taichung, 40705, Taiwan
166. Institute of Clinical Medicine, National Yang Ming University School of Medicine, Taipei 112, Taiwan
167. Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, Boston, 02446 MA, USA
168. European Genomic Institute for Diabetes (EGID), FR 3508 Lille, France
169. Centre National de la Recherche Scientifique (CNRS) UMR 8199, Lille Pasteur Institute, 1 rue du Prof Calmette, 59019 Lille Cedex, France
170. Lille 2 University, Lille, France
171. Center for Evidence-based Healthcare, University of Dresden, Medical Faculty Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany
172. Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians University, Munich, Germany
173. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-University of Munich, Munich, Germany
174. Department of Dietetics-Nutrition, Harokopio University, 70 El. Venizelou Str, Athens, Greece
175. INSERM U1142 LIMICS, UMR_S 1142 Sorbonne Universités, UPMC Université Paris 06, Université Paris 13, Paris, France
176. Department of Twin Research and Genetic Epidemiology, King's College London, London, UK
177. Department of Life and Reproduction Sciences, University of Verona, Strada le Grazie 8, 37134 Verona, Italy
178. Department of Medicine, Kuopio University Hospital, Kuopio, Finland
179. Unit of General Practice, Oulu University Hospital, Oulu, Finland
180. Department of Medicine, Program for Personalized and Genomic Medicine, University of Maryland, School of Medicine, Baltimore, Maryland 21201, USA
181. Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, 1200 Pressler St., Suite 453E, Houston, TX 77030, USA
182. Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monseratto, Monserrato, Cagliari 09042, Italy
183. Department of Cardiology, School of Medicine, University of Tampere, Tampere 33014, Finland
184. School of Medicine, University of Tampere, Tampere 33014, Finland
185. National Heart, Lung and Blood Institute, Division of Intramural Research, Bethesda, MD, USA
186. Cardiology Division, Department of Medicine, Massachusetts General Hospital
187. Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK

188. Divisions of Endocrinology and Genetics and Program in Genomics, Children's Hospital Boston, Massachusetts 02115, USA
189. Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center, Cambridge, MA 02142, USA
190. Department of Psychiatry, EMGO Institute, Neuroscience Campus, VU University Medical Centre, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands
191. Department of Psychiatry, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
192. Department of Psychiatry, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands
193. The Estonian Genome Center, University of Tartu, Estonia
194. International Centre for Circulatory Health, Imperial College London, W2 1PG, UK
195. Department of Neurology, General Central Hospital, Bolzano, 39100, Italy
196. Department of Neurology, University of Lübeck, Lübeck, Germany
197. Department of Epidemiology, University of Washington, Seattle, WA, USA
198. Department of Health Services, University of Washington, Seattle, WA
199. Group Health Research Institute, Group Health Cooperative, Seattle, WA
200. Division of Biostatistics, Washington University School of Medicine, Saint Louis, MO, 63110, USA
201. Center for Non-Communicable Diseases, Karachi, Pakistan
202. Oxford Centre for Diabetes Endocrinology and Metabolism, University of Oxford, Oxford, UK
203. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
204. Department of Nutrition, Harvard School of Public Health, Boston, MA, USA
205. Institute of Physiology, University Medicine Greifswald, Greifswald, Germany
206. Department of Biostatistics, University of Washington, Seattle, WA, USA
207. University of Ottawa Heart Institute, Cardiovascular Research Methods Centre Ontario, Canada
208. Ruddy Canadian Cardiovascular Genetics Centre, Ontario, Canada
209. National Heart, Lung, and Blood Institute, 6701 Rockledge Ave., Bethesda, MD 20892, USA
210. Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester LE3 9QP, UK
211. South Karelia Central Hospital, Lappeenranta, Finland
212. Deutsches Herzzentrum München and Technische Universität München, Germany
213. Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), München, Germany
214. Munich Heart Alliance, Germany
215. Center For Life-course Health Research, P.O.Box 5000, FI-90014 University of Oulu, Finland
216. Division of Endocrine and Metabolism, Department of Internal Medicine, Chichung Veterans General Hospital, Taichung 40705, Taiwan
217. College of Medicine, National Defense Medical Center, Taipei, Taiwan
218. Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore 117597
219. University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland
220. Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin 4, Ireland
221. Department of Haematology, University of Cambridge, Cambridge, UK
222. Department of Medicine, National University of Singapore and National University Health System, Singapore 119228, Singapore
223. Laboratory of Cardiovascular Science, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, 21224, USA
224. Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

225. Faculty of Medicine, University of Iceland, Reykjavik, Iceland
226. Department of Health Sciences, University of Leicester, University Rd, Leicester LE1 7RH, UK
227. Department of internal medicine, Erasmus MC, Rotterdam, 3000CA, The Netherlands
228. Department of Public Health and Clinical Nutrition, University of Eastern Finland, Finland
229. Research Unit, Kuopio University Hospital, Kuopio, Finland
230. Centre of Medical Systems Biology (CMSB 1-2), NGI Erasmus Medical Center, Rotterdam, The Netherlands
231. Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands
232. Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, The Netherlands
233. Sections of Preventive medicine and Cardiology, Department of Medicine, Boston University School of Medicine, Boston, 02446 MA, USA
234. Medical Population Genetics, The Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
235. Department of Pharmacology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
236. Department of Internal medicine, University Hospital Lausanne, Lausanne, Switzerland
237. Department of Epidemiology and Public Health, EA3430, University of Strasbourg, Strasbourg, France
238. Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA
239. University Medical Center Groningen, University of Groningen, Groningen, 9700RB, The Netherlands
240. Epidemiology Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston 7, Jamaica
241. Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway
242. Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway
243. MRC Cancer Unit, University of Cambridge, Cambridge, UK
244. Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 West Carson Street, Torrance, CA 90502, USA
245. Department of Epidemiology and Biostatistics, School of Medicine, Case Western Reserve University, Cleveland, OH, 44106, USA
246. Ministry of Health, Victoria, Republic of Seychelles
247. Department of Biostatistics and Epidemiology, University of Pennsylvania, USA
248. MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK
249. Enterprise Informatics, Illumina Inc., Santa Clara CA, 95050, USA
250. Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI 48109, USA
251. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA
252. Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, 9711, The Netherlands
253. Dept Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
254. Department of Medicine, Central Finland Health Care District, Jyväskylä, Finland
255. South Ostrobothnia Central Hospital, 60220 Seinäjoki, Finland

256. Red RECAVA Grupo RD06/0014/0015, Hospital Universitario La Paz, 28046 Madrid, Spain
257. Centre for Vascular Prevention, Danube-University Krems, 3500 Krems, Austria
258. Department of Medicine, Columbia University, 622 West 168th St., New York, NY 10032, USA
259. Synlab Academy, Synlab Services GmbH, P5, 7, 68161 Mannheim, Germany
260. Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, 8036 Graz, Austria
261. Unit of Primary Care, Oulu University Hospital, Kajaanintie 50, P.O.Box 20, FI-90220 Oulu, 90029 OYS, Finland
262. MRC-PHE Centre for Environment and Health, Imperial College London, London, United Kingdom
263. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, München 81377, Germany
264. Grosshadern, Klinikum, München 81377, Germany
265. The Charles Bronfman Institute for Personalized Medicine and the Mindich Child health Development Institute, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
266. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah 21589, Saudi Arabia
267. Department of Biostatistics, University of Liverpool, Liverpool L69 3GA, UK
268. Novo Nordisk Foundation Centre for Basic Metabolic Research, Section of Metabolic, Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, 2100, Denmark
269. Department of Epidemiology Research, Statens Serum Institut, 2300, Copenhagen, Denmark